REMARKS

I. Introduction

In response to the Office Action dated February 2, 2004, claims 1-10, 16-23, 33, 34 and 46-69 remain in the application. The claims have not been amended, but are presented above for the Examiner's convenience. Reconsideration of the application is respectfully requested.

II. Withdrawn Rejections and Objections

Applicants gratefully acknowledge the Examiner's indication at page 12 of the Office Action that all other rejections and objections set forth in the previous Office Action have been withdrawn. The only remaining issues are the prior art rejections discussed below, and a rejection under 35 U.S.C. §112, first paragraph, for lack of enablement, also discussed below.

III. Rejection Under 35 U.S.C. §112, First Paragraph

At page 12 of the Office Action, claims 1-5, 7-10, 16-23, 34 and 46-57 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not supported by an enabling disclosure. The rejection is based on an allegation that the specification, while being enabling for a method for eliciting an anti-tumor immune response against a pre-existing tumor in a subject, does not reasonably provide enablement for a method of prophylactically generating an anti-tumor immune response before the tumor occurs. Applicants respectfully traverse this rejection.

Example 2 of the specification, particularly at page 46, lines 25-27, and at page 47, lines 7-13, provides a working example in which colon 26 tumor cells were administered to the subjects seven days after immunization with tumor-derived hsp110. This example demonstrates tumor growth delay with prophylactic immunization in an animal model that is highly resistant to therapy. Additional guidance in prophylactic treatment is provided in the specification at pages 40-44.

The inventors have also published numerous studies that further confirm that hsp110 is of prophylactic use in a cancer model. In several of these prophylactic studies, subjects were immunized prior to transplantation with tumor: Wang et al, J. Immunol. 166:490-97, 2001; Manjili et al, Cancer Res., 62:1737-42, 2002; and Wang et al, Cancer Res., 63:2553-60, 2003 (copies provided upon request). Of particular relevance is the study of Manjili et al., J. Immunol. 171:4054-4061, 2003, that used a spontaneous mammary carcinoma model. A copy of this Manjili 2003 article is

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submitted herewith as Exhibit A. This study showed that immunization with hsp110-ICD (of Her-2) prior to the appearance of tumor at an early time significantly delays the spontaneous development of these tumors and in some cases inhibits them entirely.

Accordingly, the Examiner's assertion that the specification provides no working examples in support of prophylactic treatment of cancer is in error. In addition, further studies have confirmed that the teachings of the specification are in fact enabling for prophylactic use of hsp110 compositions. The Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. §112, first paragraph.

IV. Prior Art Rejections

At page 2 of the Office Action, claims 1-6, 16, 17, 33, 58, 59, 60, 61 and 63 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Mizzen et al. (WO 98/23735). At page 4 of the Office Action, claims 1-8, 16, 17, 33 and 58-63 were rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the combination of Mizzen and Wang et al. (FEBS Letter, 1999 February, Vol. 464, pp. 98-102). At page 6 of the Office Action, claims 1-6, 16, 17, 22, 33, 58, 59, 60, 61, 63 and 68 were rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the combination of Mizzen and Wallen (U.S. Patent No. 6,066,716). At page 7 of the Office Action, claims 1-6, 16, 17, 23, 33, 58, 59, 60, 61, 63 and 69 were rejected under 35 U.S.C. §103(a) as allegedly obvious in view of the combination of Mizzen and Srivastava et al. (WO 95/24923) and either of Dong et al. (Pharmaceutical Biotechnology, 1995, Vol. 6, pp. 625-643) or Heath (Pharmaceutical Biotechnology, 1995, Vol. 6, pp. 645-658). Applicants respectfully traverse these rejections for the reasons provided below.

1. Mizzen Does Not Anticipate the Claimed Invention

All of the rejections based on the prior art rely on the disclosure of Mizzen et al. as allegedly teaching a vaccine comprising one or more stress proteins and one or more antigens, with hsp110 as an example of a stress protein. At page 4 of the Office Action, it is alleged that "one of skill in the art would conclude without a doubt that Mizzen et al is specifically teaching that Hsp110 has the properties of a stress protein that are consistent with the composition of Mizzen et al. comprising a stress protein and an immunogenic polypeptide."

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It would be more accurate to state that one of skill in the art would conclude without a doubt that Mizzen et al. is alleging that ***any and all stress proteins*** share the same properties that would render any one of them suitable for use in a vaccine composition. One of skill in the art would not, however, conclude that this statement is true simply because it appeared in a patent disclosure. Nor could this be regarded as a disclosure that would enable one of skill in the art to select which of the numerous stress proteins listed in Mizzen et al. is in fact suitable for use in a vaccine composition beyond the bacterial stress proteins Hsp 70 and Hsp65 presented in their examples.

Mizzen et al. asserts that all of the following are suitable stress proteins for use in a vaccine composition (see pages 22-25): Hsp100-200, including Grp170; Hsp100, including mammalian Hsp110, yeast Hsp104, clpA, clpB, clpC, clpX, and ClpY; Hsp90, including *E. coli* HtpG, yeast Hsp83 and Hsc83, and human Hsp90α, Hsp90β and Grp94; *E. coli* Lon; Hsp70, including mammalian Hsp72 and Hsp73, bacterial DnaK, BiP and Grp78; Hsp60, including mycobacterial Hsp65 and bacterial GroEL; TF55, including Tcp1, TriC and thermosome; Hsp40, including prokaryotic DnaJ and mycobacterial HSJ1, HDJ1 and Hsp40; FKBPs, including FKBP12, FKBP13, FKBP25, FKBP59, Fpr1 and Nep1; cyclophilins, including cyclophilins A, B and C; Hsp20-30, including α-crystallin; *E. coli* ClpP; *E. coli* GrpE; Hsp10, including GroES and Cpn10; ubiquitin, calnexin and protein disulfide isomerases. With the exception of Hsp70 and Hsp65, no guidance is provided in the identification and selection of working embodiments amongst these 17 genuses and 45 species of stress proteins.

In order for a reference to anticipate a claimed invention, the disclosure of the reference must be enabling, and the reference must sufficiently describe the claimed invention to have placed the public in possession of it. (See MPEP §2121 and *In re Donohue* 226 USPQ 619, 621, Fed. Cir. 1985.) In an unpredictable art, one cannot extrapolate from a working example in one species to other species listed in the disclosure without undue experimentation. Such prophetic extrapolation does not amount to an enabling disclosure. (See *Adang v. Fischhoff* 62 USPQ2d 1504, 1511, Fed. Cir. 2002.)

If the Examiner's position is that Mizzen provides an enabling disclosure of a vaccine composition comprising Hsp110 and an immunogenic polypeptide, then it must be equally true that

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the Examiner is of the view that Mizzen likewise provides an enabling disclosure of a vaccine composition comprising any of the 45 species of stress proteins listed in Mizzen. Mizzen's disclosure cannot be enabling for all species of stress proteins listed therein, as it includes Grp78 and protein disulfide isomerases (page 24, line 1; and page 22, lines 20-21). Applicants' specification, at page 48, lines 7-10, demonstrates that grp78 does not exhibit the same immunogenic properties shown by the other stress proteins studied in this example. Wang et al, J. Immunol. 166:490-97, 2001, at page 496, second full paragraph (copy submitted herewith as Exhibit B), state: "Curiously, grp78, appears to be largely ineffective as a vaccine when derived from tumors." In addition, Nair et al, J. Immunol. 162:6426-32, 1999 (copy submitted herewith as Exhibit C), examine five stress proteins: calreticulin, grp94 (gp96), grp78 (BiP), ERp72, and protein disulfide isomerase (PDI); for immune activity. While calreticulin and grp94 exhibit the ability to stimulate cytolytic T cells, they report that "Little or no activity was observed for BiP, ERp72 and, protein disulfide isomerase." This report by Nair et al. illustrates the unpredictability of the stress protein art. The finding that Grp78, one of the few stress proteins of those listed by Mizzen et al. that have actually been tested for vaccine activity, is not immunogenic further confirms that stress proteins involve an unpredictable art.

Moreoever, to the extent that Mizzen discloses the use of a heat shock protein in combination with an immunogenic polypeptide, this reference does not teach specifically that hsp110 has therapeutic properties. Although hsp110 is mentioned as an example of a heat shock protein, no basis for expecting the structurally dissimilar hsp110 to have the same immunogenic utility as, for example hsp70, is provided. Because one of ordinary skill in the art would not have had a reasonable expectation of success with a pharmaceutical vaccine composition comprising isolated hsp110 complexed with an immunogenic polypeptide in the absence of data demonstrating the ability to elicit an effective immune response, none of the cited references discloses the claimed invention, and none provides an enabling disclosure (see MPEP §2121).

Applicants' specification provides additional reasons why one skilled in the art would not have extrapolated the data reported by others regarding hsp70 or hsp65 to hsp110 or grp170. The specification discusses at page 2, lines 23-30, the lack of information available about the function and activity of the larger stress proteins, hsp110 and grp170. As stated in Applicants' specification at page 3, lines 1-2, "[n]ot all stress proteins function as vaccines, however, and it can be expected that

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different ones may exhibit different activities." This statement that one cannot presume all stress proteins function as vaccines is supported by the specification's disclosure at page 48, lines 7-10, that grp78 failed to exhibit the same immunogenic properties as shown by the other stress proteins studied in this example, as well as the references cited above. Accordingly, the mere fact that hsp110 had been identified as a stress protein was not enough to indicate that it could be used to inhibit cancer or other disease, and Mizzen et al. did not put the public in possession of a vaccine composition comprising hsp110 and an immunogenic polypeptide.

Applicants have demonstrated that two of the three stress proteins described in their examples (hsp110 and grp170, but not grp78) do in fact exhibit remarkable and effective immunogenic properties and function effectively as vaccines for the treatment and prevention of cancer. The discovery that hsp110 and grp170 are even better chaperones than hsp70 was surprising and unexpected given the divergence in size and sequence between hsp70 and these larger stress proteins. As noted at page 16, lines 16-17 and 23-24, of the specification, hsp110 is more than just another alternative to hsp70. Rather, hsp110 is capable of binding much larger polypeptides than can hsp70, and binds with greater efficiency, which is particularly surprising given the extent to which it diverges from the structure and function of hsp70.

2. *Wallen Erroneously Confuses Hsp104 With the Hsp110/105 Family*

The rejection at pages 6-7 of the Office Action relies on U.S. Patent 6,066,716 to Wallen as teaching a method of heating heat shock proteins, including Hsp110 because Wallen teaches incubation between 37-50 degrees increases the number of heat shock proteins and teaches that members of the hsp104-105 family are particularly useful, with hsp110 identified as a member of this family. This use of Wallen is erroneous for the following reasons.

As argued previously, Wallen teaches a method of purifying heat shock proteins that is not applicable to hsp110 because Wallen's method uses binding to ADP and hsp110 does not bind ADP or ATP. The reference to Figure 4 of Oh et al. in support of this fact was regarded as not persuasive because examination of the legend for Figure 4B indicates a column marked "beads" showing proteins remaining on the ATP agarose after ATP elution. This is correct. However, an expression system was used, resulting in overexpressed protein that is improperly folded and capable of non-specific interaction. The data in Figures 4A and 4B of Oh indicate that some recombinant

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hsp110 binds non-specifically to agarose beads. The fact that it is not eluted by ATP indicates that binding is non-specific. This is further born out by the fact that, when hsp110 is exposed to the agarose beads in the presence of excess ATP, binding still occurs, meaning that the binding is ATP-independent and non-specific. Others have examined ATP binding ability of hsp105 (another name for hsp110) by agarose column chromatography and found the protein did not bind (Yasuda et al., J. Biol. Chem., 270:29713-23, 1995).

Although Wallen teaches that members of the hsp104-105 family are particularly useful and identifies hsp110 as a member of this family, Applicants respectfully note that Wallen is confusing hsp104 with hsp105. Hsp104 is a separate family of stress proteins with no homology to the hsp105/110 family (Lee-Yoon et al, J. Biol. Chem. 270:15725-33, 1995; also see GenBank Database). Hsp104 does not exist in mammals (unlike hsp105/110) and has an entirely different sequence, function and distribution.

3. *Wallen Suggests Heating the Lysate, Not an Isolated Complex*

Wallen et al. is cited as teaching incubation between 37 and 50 degrees to increase the number of heat shock proteins. This teaching involves heating the cellular lysate (meaning mixture of hsp and antigen together with additional cellular material). The resultant increase of mRNA for some heat shock proteins leads to an increase in cellular levels (number) of heat shock proteins. The invention of Applicants' claims 22 and 68 concerns the function of hsp110, and is not related to the increase in numbers of some of these proteins that can occur by heat shock due to altered gene expression.

The subject matter of claims 22 and 68 relates to an intrinsic function of hsp110 that enables it to form a "chaperone complex" with a denatured substrate protein. Heat shock is one method used to denature the substrate protein. While in the chaperone complex, the substrate protein is protected from aggregation and can be refolded. This has nothing to do with the quantity of or number of hsp present that is secondary to heat-induced gene expression. Wallen et al., by suggesting heating of the cellular lysate, does not suggest ***heating the isolated stress protein complex*** to enhance binding of the hsp110 polypeptide to the immunogenic polypeptide, as required by claims 22 and 68.

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Because none of the 6 references cited in the Office Action, taken alone or in combination, teaches that hsp110 is capable of eliciting an immune response, these references cannot teach or suggest a pharmaceutical vaccine composition comprising an isolated stress protein complex comprising hsp110 and an immunogenic polypeptide nor can they teach or suggest use of such a composition for inhibiting cancer or tumor growth. All of the prior art rejections rely on Mizzen, which cannot anticipate the dozens of species listed therein without an enabling disclosure.

V. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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